

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 22-33, 35-51, 53, 55-70, 72, 75-81, 84-89, 92-105, 108-114, 118, 120-124, 126-141, 144-152, 156, 158-161, 165-173, 176-195, and 198-219 are pending in the application, with claims 22, 48, 68, 85, 102, 120, 139, 157, 178, 194, and 209 being the independent claims. The Examiner has allowed claims 22, 24-43, 48, 50, 51, 55-63, 68, 70, 71, 75-81, 85, 87, 88, 92-98, 139, 140, 144-152, and 178-191. The Examiner has withdrawn claims 46, 66, 117, 137, 155, 176, 192, and 207 from consideration due to a restriction requirement. Claims 17, 19, 34, 52, 54, 71, 73-74, 82, 83, 90, 91, 106, 107, 115-117, 119, 125, 142-143, 153-155, 157, 162-164, 174-175, 196, and 197 are sought to be canceled without prejudice to or disclaimer of the subject matter thereof. Applicants reserve the right to pursue the subject matter of these claims in related applications. These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview With the Examiner

Applicants would like to thank Examiner Claire Kaufman for the courtesy extended in the telephonic interview on July 27, 2000 with Patent Agent Elizabeth J. Haanes. The amendments and remarks herein were discussed during the interview.




Support for the Amendments

The specification has been amended to make proper reference to the formal drawings submitted herewith. The claims have been amended for clarity, and to more particularly point out and distinctly claim the subject matter Applicants regard as the invention. Applicants assert that these amendments present no new matter. Entry of these amendments is therefore respectfully requested.

The Statement Concerning the Deposited cDNA Clone

The Examiner has maintained a previous rejection under 35 U.S.C. § 112, first paragraph to those claims reciting ATCC Deposit No. 97853, stating that the executed Statement Concerning the Deposited cDNA clone did not accompany the Amendment and Reply filed on November 23, 1999. *See* Paper No. 12 at page 8. Further, the Examiner asserts that a copy of said Statement likewise did not accompany the Amendment and Reply filed on August 1, 2000. This rejection pertains to pending claims 120-124 and 126-138.

Applicants respectfully maintain that a Statement Concerning the Deposited cDNA clone executed by James H. Davis was submitted with the Amendment and Reply filed on November 23, 1999. In support of this, a copy of the Statement Concerning the Deposited cDNA clone filed on November 23, 1999, as well as a copy of the stamped post-card receipt which lists this document as received by the P.T.O. on that date was attached to the Amendment and Reply filed on August 1, 2000. Yet another copy of these documents, as well as a copy of the stamped post-card receipt listing the documents as received by the P.T.O. on August 1, 2000, are attached



hereto. If the Examiner is still requires copies of these documents, the copies will be hand-carried to the Examiner directly upon request to the undersigned Agent.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Restriction Requirement

The Examiner has stated the claims 46, 66, 117, 137, 155, 176, 192, and 207 embody subject matter which is distinct from the invention originally claimed. *See* Paper No. 12 at page 2.

Claims 117 and 155 have been canceled. Applicants reserve the right to pursue the subject matter of these claims in related applications. With respect to claims 46, 66, 137, 176, 192, and 207, Applicants respectfully traverse, and submit that to search and examine the subject matter of these claims together with the remainder of the pending claims would not be a serious burden on the Examiner. For example, publications which disclose host cells comprising TNF-family receptors normally also disclose that such host cells are useful to screen for ligand binding, thereby making it a simple matter for the Examiner to search and examine a method to screen for ligand binding utilizing host cells of the present invention. The M.P.E.P. § 803 (Seventh Edition, Rev. July, 1998) states:

If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, in view of the M.P.E.P. § 803, Applicants respectfully request that claims 46, 66, 137, 176, 192, and 207 be searched and examined in the subject application.

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Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

However, while not acquiescing to the Examiner's restriction requirement, Applicants note that the claims 46, 66, 137, 176, 192, and 207 are related to the elected claims as between a product and a process for using the product, and further, that the process of claims 46, 66, 137, 176, 192, and 207 depend from and include all the limitations of the product of claims from which they depend, *i.e.*, claims 44, 65, 135, 172¹, 190, and 205, respectively. In light of the decisions in *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ 2d 1663 (Fed. Cir. 1996), a notice was published in the Official Gazette which set forth new guidelines for the treatment of product and process claims. *See* 1184 OG 86 (March 26, 1996). Specifically, the notice states that

in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim depends from or otherwise includes all the limitations of an allowed product claim.

Id. Claim 190 has been allowed. Accordingly, Applicants respectfully request that claim 192 be rejoined and examined for patentability. Furthermore, Applicants respectfully request that if any of claims 44, 65, 135, 172, and 205 are found allowable, that claims 46, 66, 137, 176, and 207 be rejoined and examined for patentability.

¹Claim 174, from which claim 176 currently depends, has been canceled. However, upon rejoinder, claim 176 would be amended to depend from claim 172.

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Rejection under 35 U.S.C. § 112, Second Paragraph

(a) The Examiner has rejected claims 23, 34-36, 49, 52-54, 69, 72-74, 86, 89-91, 103, 106-107, 121, 125-127, 141, 159, 162, 194, and dependent claims 44, 45, 47, 64, 65, 57, 82-84, 99-101, 115, 116, 119, 135, 136, 138, 153, 154, 156, 163, 174, 175, 177, 195-206, and 208 under 35 U.S.C. § 112, second paragraph, alleging that the phrase "said nucleic acid" is indefinite, in that the independent claims refer to a nucleic acid and a "reference nucleic acid." *See* Paper No. 12 at page 3-4. The Examiner has stated that the amendments proposed in the Amendment and Reply filed on August 1, 2000 would alleviate this rejection. *See* Paper No. 19 at page 3. Those amendments and the accompanying remarks are reiterated herein.

While not acquiescing to the Examiner's rejection, in order to expedite allowance of claims, Applicants have amended independent claims 22, 48, 68, 85, 102, and 120 to recite a "first" and a "second" nucleic acid, and have amended the corresponding dependent claims to refer back to either the "first" or "second" nucleic acids so named. Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

(b) The Examiner has rejected those claims referring to "a TNF ligand" *i.e.*, claims 34, 52, 72, 90, 106, 125, 141, 162, and 194, under 35 U.S.C. § 112, second paragraph, stating that it is unclear what a TNF ligand is. *See* Paper No. 12 at page 4. The Examiner has stated that the amendments proposed in the Amendment and Reply filed on August 1, 2000 would alleviate this rejection. *See* Paper No. 19 at page 3. Those amendments and the accompanying remarks are reiterated herein.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 34, 52, 72, 90, 106, 125, and 162, have amended claims 72 and

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141 simply to state that the claimed polynucleotide encodes a polypeptide, and have amended claim 194 to refer to a polypeptide which binds TRAIL. Applicants reserve the right to pursue the canceled claims in related applications. Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

(c) The Examiner has rejected claim 159 under 35 U.S.C. § 112, second paragraph, alleging "it is unclear if the "nucleic acid" of the claim is intended to be the same as or in addition to the "nucleic acid" of claim 157, upon which it depends." *See* Paper No. 12 at page 4. The Examiner has stated that the amendments proposed in the Amendment and Reply filed on August 1, 2000 would alleviate this rejection. *See* Paper No. 19 at page 3. Those amendments and the accompanying remarks are reiterated herein.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, applications have amended claim 159 to recite "wherein said nucleic acid encodes amino acids 132 to 221 of SEQ ID NO:2." Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

(d) The Examiner has stated that the amendment proposed for claim 101 in the Amendment and Reply filed on August 1, 2000 would allegedly render the claim confusing because it is not clear what the antecedent basis for "said nucleic acid" is. *See* Paper No. 19 and page 3.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 101 to depend from claim 89, which clearly recites a polynucleotide which encodes a polypeptide. Therefore the polypeptide and polynucleotide of claim 101 have their antecedent basis in claim 89. Solely for the sake of clarity and consistency,

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Applicants have made analogous amendments to claims 47, 67, 84, 118, 138, 156, 177, 193, 208, and 219.


In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 112, second paragraph, as applied to the pending claims.

Rejections under 35 U.S.C. § 112, First Paragraph

In Paper No. 19, the Examiner stated that claim 68 would "remain" rejected under 35 U.S.C. § 112, first paragraph (even though it was listed as allowed in Paper No. 12) "for not being enabled for how to use a nucleic acid which is 90% identical to a nucleic acid encoding a relatively small fragment . . . of SEQ ID NO:2." *See* Paper No. 19 at page 2.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, applicants have amended claim 68 recite a nucleic acid which is at least 90% identical to nucleotides 733 to 810 of SEQ ID NO:1. Therefore, degeneracy of the genetic code is accounted for because the 90% identity must be at the nucleotide level. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

In Paper No. 19, the Examiner has stated that proposed claim 89 would remain rejected under 35 U.S.C. § 112, first paragraph, because "the domain shown to be required for apoptosis . . . is only limited to that which is 90% identical to amino acids encode[d] by a nucleic acid encoding amino acids 265-468 of SEQ ID NO:2 . . . , [and] in the claim upon which 89 depends (claim 85), the first nucleic acid does not need to encode anything, let alone a polypeptide that allows for apoptosis to occur. *See* Paper No. 19 at page 2.



Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 89 to require that said first nucleic acid encode a polypeptide. With respect to whether polypeptides, encoded by the claimed polynucleotides, which are 90% identical to amino acids 265-468 of SEQ ID NO:2, and which function within a full length DR4 polypeptide to induce apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells, Applicants respectfully traverse, as set forth in the arguments below regarding claims 127, 89, and 102.

The Examiner has rejected "claims requiring the ability to encode a polypeptide that induces apoptosis or binds a TNF ligand or TRAIL and claims depending thereon . . . excluding claims 35-36, 126-127, and including claims dependent on claim 194 which are complementary to a coding sequence . . ." under 35 U.S.C. § 112, first paragraph. *See* Paper No. 12 at page 5. Further, the Examiner has rejected claims where the polynucleotide comprises "a nucleic acid at least 90% identical to a reference nucleic acid encoding a fragment of SEQ ID NO:2 where the fragment is not enabled or where the nucleic acid cannot be used commensurate in scope with the instant invention" under 35 U.S.C. § 112, first paragraph. *See Id.* The Examiner alleges that the specification does not provide enablement for polynucleotides encoding less than the full extracellular domain that bind a TNF ligand or TRAIL or less than the full-length or mature polypeptide which induces apoptosis. *See* Paper No. 12 at page 4-7. In a telephonic interview with Patent Agent Elizabeth J. Haanes on July 28, 2000, the Examiner further noted that claims directed to "a method to produce a polypeptide," *e.g.*, pending claims 47, 67, 84, 138, 156, 177, 193, and 208, are rejected for lack of enablement, apparently because applicants allegedly have not indicated the specific polypeptide to be produced, or its function.

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The Examiner gives as examples of claims included in this portion of the rejection claims "34, 36, 44, 45, 47, 53-54, 64, 65, 67, 72-74, . . . 102-116, 118, 119, . . . 194 . . . , excluding claims 35-36, 126-127" See Paper No. 12 at page 4. Based on these examples, Applicants have deduced that the claims the Examiner intends to include in this portion of the enablement rejection consist of claims 34, 44, 45, 47, 52-54, 64, 65, 67, 72-74, 82-84, 89-91, 99-101, 102-116, 118, 119, 125, 135, 136, 138, 141-143, 153, 154, 156, 162-164, 174, 175, 177, 193-206, and 208 only. In Paper No. 19, the Examiner stated that this deduction was correct.


Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 34, 52, 54, 73-74, 82, 83, 90, 91, 106, 107, 115-117, 119, 125, 142-143, 153-155, 162-164, 174-175, 196, and 197, directed to polynucleotides with certain functional limitations, have amended claims 72 and 141 simply to state that the claimed polynucleotide encodes a polypeptide, have amended claims 194 and 195 to specify that the claimed polynucleotide hybridizes to the complementary strand, and have amended claims 47, 67, 84, 101, 118, 138, 156, 177, 193, and 208 to specify a method of producing a polypeptide encoded by a claimed nucleic acid. With respect to the pending claims, as amended, Applicants respectfully traverse.

Under the Federal Circuit standard for enablement, some necessary experimentation by the skilled artisan is permitted; the amount of experimentation, however, must not be unduly extensive. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Furthermore, patent claims that include some claimed combinations which are inoperative are not necessarily invalid under 35 U.S.C. § 112. *Id.* As the Examiner has pointed out, factors to be considered when determining whether the amount of experimentation is undue were set out in *In re Wands*, 858 F.2d 731 at 737 (Fed. Cir. 1988). See Paper No. 12 at page 5.

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The full extracellular domain of the DR4 polypeptide is described in the Specification to be amino acids 24 to 238 of SEQ ID NO:2. *See* the specification at page 10, lines 23-24. Accordingly, the full extracellular domain of the DR4 polypeptide is recited in claim 53. Claim 126, as amended, refers to a polynucleotide encoding the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No 97853 which has the ability to bind TRAIL. Claim 194, as amended, recites a polynucleotide comprising a nucleic acid which hybridizes to the complement of nucleotides 88 to 732 of SEQ ID NO:1, wherein the nucleic acid encodes a polypeptide which binds TRAIL. The Examiner has stated that the captioned application provides enablement for the full DR4 extracellular domain binding TRAIL. For support see *e.g.*, specification at page 8, lines 1-13 and Figure 6. Since each of claims 53, 126, and 194 recite certain polynucleotides which encode the full DR4 extracellular domain, claims 53, 126, and 194 each include specific embodiments which are enabled by disclosure of the present application.


In Paper No. 19, however, the Examiner has maintained the rejection under 35 U.S.C. § 112, first paragraph, alleging that "inclusion in the specification of methods for testing . . . provides an invitation to experiment without supportive information in the specification that provides a reasonable expectation of success without undue experimentation" *See* Paper No. 19 at pages 3-4. Applicants maintain that only routine experimentation is required, and therefore, claims 53, 126, and 194 are enabled for their full scope using the rule set out in *Atlas Powder and Wands*. Given (a) the teachings of the present application, (b) the ease in screening large numbers of polypeptides for ligand binding in a single experiment, and (c) the high level of skill in the art regarding both the structure of TNF-family receptors and the functional domains required for TNF-family receptor/ligand interactions, one of ordinary skill in the art could routinely make and



use polynucleotides according to these claims which encode a polypeptide which binds TRAIL, without undue experimentation.

Two factors to be considered in determining whether undue experimentation is required are "the amount of direction or guidance presented," and "the predictability or unpredictability of the art." *See Wands* 8 USPQ2d 1400 at 1404. The specification teaches, at page 1, line 21 through page 4, line 2, and in the references cited therein, that a great deal is known about the ligand-binding domains of TNF-family receptors. For example, it is well known that specific conserved cysteine residues play an important role in ligand binding. Figure 2 shows a comparison of the amino acid sequences of four different TNF-family receptors, including DR4, which illustrates the conserved amino acids in the ligand binding extracellular domain important for TNF-family ligand binding activity. Accordingly, one of ordinary skill in the art could compare the deduced amino acid sequences of the ligand binding domains of the several TNF-family receptors and thereby reasonably predict which conserved amino acids are required for ligand binding.

Additional factors to be considered in determining whether undue experimentation is required are "the state of the prior art," and "the quantity of experimentation necessary." *See Id.* At the time of filing, the TNF-family ligand TRAIL had been isolated and characterized. *See* specification at page 3, line 22 through page 4, line 15, and the cited references therein. Accordingly, the TRAIL ligand was readily available for use in ligand binding assays. The specification further teaches: methods to screen for ligand binding (page 31, line 3 through page 32, line 28), conservative amino acid substitutions (page 23, line 37 through page 25), and methods of mutagenesis to generate polypeptides with amino acid substitutions (page 25, lines 4-13). At the time of filing, testing of large numbers of variant polypeptides for the effect on



ligand binding was routine. *See, e.g.,* Breyer, *et al.* *EMBO J.* 9:2679-2684 (1990), attached hereto as Exhibit A, and Perez *et al.*, *J. Biol Chem.* 269:22485-22487 (1994), attached hereto as Exhibit B. It is clear from these references that the entire process of generation of multiple mutants and their screening for ligand binding is considered by the skilled artisan as a single "experiment," much as the the entire attempt to generate and screen monoclonal antibodies having a particular activity was considered a single "experiment " in *Wands*. *See* 8 USPQ2d 1400 at 1407. Thus, the quantity of experimentation is not unreasonable. Furthermore, as these references demonstrate, in screening large numbers of mutants, practitioners expect to screen a certain proportion of negative samples, similar to the screening of large numbers of hybridomas discussed in *Wands*. *See Id.* at 1406. Finally, commercial kits for site-directed mutagenesis were readily available, which further demonstrates that this aspect of screening is routine. *See, e.g.,* the pages from the 1996 Promega Catalog, the 1995, New England Biolabs Catalog, and the 1995 Life Technologies, Inc. Catalog, attached hereto as Appendix C.


Given the high level of skill in the art regarding the structure of TNF-family receptor ligand binding domains, and the teachings in the specification as to which amino acids must be conserved, methods to make conservative substitutions, and how to test for TRAIL binding, it would be a simple matter of routine experimentation for one of ordinary skill in the art to determine which polynucleotides actually encode a polypeptide capable of binding TRAIL. Since the skilled artisan has clear guidance as to which polynucleotides predictably will encode a polypeptide that will bind TRAIL, and only routine experimentation is required to screen for TRAIL binding, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

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Therefore, the specification is fully enabling for the polynucleotides recited in claims 53, 126, and 194.

Claim 127, as amended, recites a polynucleotide comprising a first nucleic acid at least 90% identical to a second nucleic acid encoding the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 97853, wherein the first nucleic acid encodes a polypeptide which induces apoptosis. The Examiner has stated that Example 5 provides enablement for the full-length receptor inducing apoptosis. *See* Paper No. 12 at page 6, *see also*, Figure 5 and page 8, lines 7-10 of the captioned application. Upon expression in eukaryotic cells, a full-length cDNA clone contained in ATCC Deposit No. 97853 would express the mature DR4 amino acid sequence on the surface of the cells. Since claim 127 recites certain polynucleotides which encode the mature DR4 polypeptide, claim 127 includes specific embodiments which are enabled by disclosure of the present application.


In Paper No. 19, however, the Examiner has maintained the rejection under 35 U.S.C. § 112, first paragraph, alleging that "inclusion in the specification of methods for testing . . . provides an invitation to experiment without supportive information in the specification that provides a reasonable expectation of success without undue experimentation" *See* Paper No. 19 at pages 3-4. Applicants maintain that only routine experimentation is required, and therefore, claim 127 is enabled for its full scope using the rule set out in *Atlas Powder and Wands*. Given (a) the teachings of the present application, (b) the ability to screen large numbers of polypeptides for their ability to induce apoptosis in a single experiment, and (c) the high level of skill in the art regarding TNF-family receptor death domains, one of ordinary skill in the art could routinely make and use the claimed polynucleotides which encode polypeptides which induce apoptosis, without undue experimentation.



Factors to be considered in determining whether undue experimentation is required are "the amount of direction or guidance presented," "the presences or absence of working examples," "the predictability or unpredictability of the art," "the state of the prior art," and "the quantity of experimentation necessary." *See Wands* 8 USPQ2d 1400 at 1404. With respect to the state of the prior art, the specification teaches, at page 2, line 1 to page 3, line 21, and in the references cited therein, that a great deal is known about the death domains of TNF-family receptors. Figure 2 provides sound guidance by showing a comparison of the amino acid sequences of four different TNF-family receptors, including DR4, which illustrates conserved amino acid regions throughout the respective polypeptides, including the death domain regions important for induction of apoptosis. Accordingly, one of ordinary skill in the art could compare the deduced amino acid sequences of the several TNF-family receptors which induce apoptosis, and in particular, the death domains, to reasonably predict which conserved amino acids are required for the induction of apoptosis.

The specification further teaches: a working example demonstrating a method to screen for apoptosis (Example 5), conservative amino acid substitutions (page 23, line 37 through page 25), and methods of mutagenesis to generate polypeptides with amino acid substitutions (page 25, lines 4-13). As mentioned *supra*, the generation of mutant polypeptides with known substitutions is routine, and a large number can be generated in a single experiment. Furthermore, at the time of filing, kits were commercially available to screen large numbers of polypeptides in a single experiment for their ability to induce apoptosis, making this aspect of the experiment routine. *See, e.g.*, the pages of the 1995 BMB Catalog attached hereto as Exhibit D.

Given the high level of skill in the art regarding the structure of TNF-family receptor death domains, and the teachings in the specification as to: which amino acids should be conserved in



the death domain and elsewhere in the polypeptide; methods to make conservative substitutions; and how to test for apoptosis; it would be a simple matter of routine experimentation for one of ordinary skill in the art to determine which polynucleotides encode polypeptides which induce apoptosis. Since the skilled artisan has clear guidance as to which polynucleotides will encode a polypeptide that will induce apoptosis, and only routine experimentation is required to screen for apoptosis, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

Therefore, the specification is fully enabling for the polynucleotides recited in claim 127.

Claims 89 and 102, as amended, recite isolated polynucleotides comprising a first nucleic acid at least 90% identical to a second nucleic acid encoding various polypeptide fragments of SEQ ID NO:2, wherein a DR4 variant consisting of amino acids 24 to 468 of SEQ ID NO:2, with the exception that amino acids 265-468 of SEQ ID NO:2 (in claim 89) or amino acids 379 to 422 of SEQ ID NO:2 (in claim 102) are deleted and replaced with a polypeptide encoded by said first nucleic acid, induces apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells. One of ordinary skill in the art would readily understand from the specification and the art existing at the time of filing that a mature DR4 polypeptide comprising the claimed polypeptide fragment would have to include a polypeptide domain with death domain activity. For example, the nucleic acid would be related to a fragment of the polynucleotide comprising nucleotides 1153-1284 of SEQ ID NO:1, which encodes the DR4 death domain. As noted above in the remarks relating to claim 127, additional structural features required for the induction of apoptosis in the DR4 variant comprising the polypeptide can be predicted based on the existing art and the disclosure provided in the present application. The specification further discloses the routine experimental methods to screen for apoptosis *in vitro* by overexpression in human 293 embryonic

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kidney cells. Furthermore, as mentioned above, other assays were readily available in kit form for routine screening of large numbers of polypeptides for their ability to induce apoptosis. Therefore, as with claim 127, one of ordinary skill in the art could easily discern those polynucleotides encompassed by claims 89 and 102 which encode a polypeptide which, when substituted into a DR4 variant, will allow that DR4 variant to induce apoptosis in the stated *in vitro* test. Since the skilled artisan has clear guidance as to which DR4 variants comprising the claimed polypeptide will induce apoptosis, and only routine experimentation is required to screen for apoptosis in the stated *in vitro* test, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 112, first paragraph, as applied to the pending claims.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claim 157 under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AA100865. *See* Paper No. 12 at page 8, and Paper No. 19 at page 3.

Solely to advance prosecution, and not in acquiescence of the Examiner's rejection, Applicants have canceled claim 157. Applicants maintain that the arguments presented in the Amendment and Reply dated August 1, 2000, *i.e.*, are valid, and reserve the right to pursue the subject matter of claim 157 in related applications. In addition, Applicants have amended claim 158 to be independent, amended claims 159, 160, 161, 165, 169, 170, and 172 to depend from claim 158, and have added claims 209-219.

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The Federal Circuit has stated that "[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention" *Hybritech Incorporated v. Monoclonal Antibodies, Inc.* 231 U.S.P.Q. 81, 90 (Fed. Cir., 1986).

Claims 209-219 require that the claimed polynucleotide include a nucleic acid which encodes at least 30 contiguous amino acids from 1 to 238 of SEQ ID NO:2, and that the nucleic acid be operably associated with regulatory elements capable of directing the translation of those amino acids. GenBank Accession No. AA100865 includes no such regulatory elements. Therefore, claims 209-219 are novel and non-obvious over GenBank Accession No. AA100865. Based on these remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a).

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Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Elizabeth J. Haanes
Agent for Applicants
Registration No. 42,613

Date: August 31, 2000

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

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